REMARKS

Claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42, and 78 are pending. Claims 67-76 have been withdrawn as directed to a non-elected invention. Accordingly, claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42, and 78 are presently being examined.

APPLICANTS' CLAIMED INVENTION

The claimed invention provides the following.

A method for inhibiting T cell proliferation comprising contacting CD28 positive T cells with B7 antigen so as to bind the CD28 receptor on the CD28 positive T cells with B7 antigen and thereby inhibiting T cell proliferation.

A method of **inhibiting CD28 positive T cell proliferation** comprising reacting B7 positive cells with a monoclonal antibody designated BB-1 or a $F(ab)_2$ fragment thereof or the CD28Ig fusion protein **so as to bind the monoclonal antibody or the $F(ab')_2$ fragment thereof or the CD28Ig fusion protein with B7 positive cells** and thereby blocking B7-T cell interaction and inhibiting CD28 positive T cell proliferation.

A method for preventing the binding of the CD28 receptor to the B7 antigen comprising **contacting CD28 positive T cells with an anti-CD28 monoclonal antibody** which recognizes and binds a determinant site to which the monoclonal antibody 9.3 is directed so as to prevent binding of the receptor to the B7 antigen.

A method for preventing the binding of the CD28 receptor to the B7 antigen comprising **contacting CD28 positive T cells with a fragment or derivative of the extracellular domain of the B7 antigen so as to bind the CD28 receptor on the CD28 positive T cells with the fragment or derivative of the extracellular domain of the B7 antigen** thereby preventing binding of the receptor to the B7 antigen.

The claimed methods provide the use of monoclonal antibodies directed against B7 or CD28 antigens, B7Ig and CD28Ig fusion proteins, or fragments thereof, each having the characteristic described in the claim.

REJECTION UNDER 35 U.S.C. §101

At page 2, paragraph 23, of the Office Action, the Patent Office rejected claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42 and 78 under 35 U.S.C. §101 because the invention as disclosed is allegedly inoperative and would therefore lack utility.

The Patent Office has taken the position that there is no evidence which clearly and reproducibly illustrates that there is any utility for the claimed invention because antibodies have had very limited success as described in the Harris, Waldmann, Dillman, Osband, and Hird references.

Since the Patent Office has challenged only the operability of monoclonal antibodies in therapy, it appears that the operability of B7 antigen, the B7Ig fusion protein, or the CD28Ig fusion protein remains unchallenged. Therefore, applicants contend that the Patent Office is not challenging methods of the invention which are directed to the use of B7 antigen, the B7Ig fusion protein, and the CD28Ig fusion protein.

Applicants respectfully traverse the rejection with regard to the claimed methods' use of monoclonal antibodies for the reasons which follow.

THE REJECTION IS BASED ON FACTUALLY FALSE ASSUMPTIONS

Contrary to the Patent Office's position, the potential for the in vivo clinical use of monoclonal antibodies has been firmly established (Thorpe "Monoclonal antibodies: Clinical and regulatory issue" Tibtech February 1993 (vol. 11) pp. 40-43 which will be provided shortly; Dillman at page 592, left column, Hird at page 185, second full paragraph, fourth sentence; Arnon et al. "Monoclonal antibodies for immunotargeting of drugs in cancer therapy" Monoclonal Antibody and Cancer Therapy, pages 243-256, Abstract at page 243, bottom of the page, Alan R. Liss, Inc. (1985) already of record as Exhibit DE in applicants' Information Disclosure Statement).

For example, the consensus of attendees of the meeting "Monoclonal antibodies: Clinical and regulatory issues" was that monoclonal antibodies are useful as therapeutic agents and in vivo diagnostic agents (Thorpe, supra). Further, radiolabeled monoclonal antibodies recognizing B-lymphocyte surface antigens represent a potentially effective new therapy for lymphokines (Press et al. which will be provided shortly).

THE LEGAL STANDARD FOR UTILITY

Utility must be definite and in currently available form, not merely for further investigation or research[1]. However, establishment of commercial usefulness is unnecessary[2].

The Supreme Court defined the "operability requirement" in

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[1] Brenner v. Manson, 383 U.S. 519, 148 U.S.P.Q. 689 (U.S. 1966).

[2] In re Langer, 503 F.2d 1380, 183 U.S.P.Q. 288 (CCPA 1974).

holding that a new product or process, to be patentable, must be shown to be "capable of being used to effect the object proposed" in a patent application[3].

The burden of proving operability and utility shifts to the applicant only if there is a reasonable doubt as to the truth of the applicant's assertions--**not just any doubt**[4]. The claim of non-utility cannot be sustained without proof of total incapacity[5].

By taking the position that generally monoclonal antibodies used in primarily cancer therapy have not been efficacious in clinical trials as evidenced by the cited references, the Patent Office is implementing a "commercial success" standard for 35 U.S.C. § 101 which has been rejected by the courts. Specifically, the courts

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[3] Mitchell v. Tilghmam, 86 U.S. 287 (1873).

[4] In re Bundy, 209 USPQ 48 (CCPA 1981); In re Gazave, 154 USPQ 92 (CCPA 1967); In re Chilowsky, 109 USPQ 321 (CCPA 1956).

[5] E.I. Dupont Nemours and Company v. Berkeley and Company, 620 F.2d 1247, In Dupont, the plaintiff's patent was upon a fishing line containing fluorescent dye. The object of the invention was to make the line visible to fishermen above the water but invisible to fish below the water. The defendant introduced evidence tending to show that the line remained visible under many water conditions. The Eighth Circuit held that the defendant's evidence failed to even raise an issue of lack of utility for the jury since perfection under all conditions is not required, whether the patent does or does not suggest that the invention is imperfect or inoperable under certain conditions. A small degree of utility is sufficient. The claimed invention must only be capable of performing some beneficial function. An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely. A commercially successful product is not required nor is it essential that the invention accomplish all its intended functions or operate under all conditions, partial success being sufficient to demonstrate patentable utility.

have stated that "full scale clinical trials in humans ...may be necessary to establish "commercial usefulness" in this technology. However, commercial usefulness is not within the meaning of § 101".

Proof of utility under this section may be established by animal in vivo data or in vitro data, or combinations of these[6],[7].

As stated by the Patent Office in the Proposed Utility Examination Guidelines published in the January 30, 1995 edition of the Federal Register, the courts in In re Krimmel[8], and In re Sichert[9] specifically rejected the position of the Patent Office that testing in animals was not relevant to establishing utility of claims to methods for treating humans.

Proof of operability requires only presentation of evidence that as of the effective filing date of the application a person of skill in the pertinent art would have concluded that the claimed invention would likely be effective to some extent for a purpose described for the invention in the application, as the application would have been understood by such a person on the

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[6] In re Irons, 340 F.2d 924, 144 U.S.P.Q. 351 (CCPA 1965); Ex parte Paschall, 88 U.S.P.Q. 131 (Bd. App. 1950); Ex parte Pennell et al., 99 U.S.P.Q. 56 (Bd. App. 1952); Ex parte Ferguson, 117 U.S.P.Q. 229 (Bd. App. 1957); Ex parte Timmis, 123 U.S.P.Q. 581 (Bd. App. 1959); Ex parte Krepelka, 231 U.S.P.Q. 746 (Bd. Pat. App. & Inter. 1986); Ex parte Chwang, 231 U.S.P.Q. 751 (Bd. Pat. App. & Inter. 1986).

[7] In re Hartop et al., 311 F.2d 249, 135 U.S.P.Q. 419 (CCPA 1962); Ex parte Murphy, 134 U.S.P.Q. 134 (Bd. App. 1960); Ex parte Timmis, 123 U.S.P.Q. 581 (Bd. App. 1959).

[8] 230 USPQ 215 (CCPA 1961).

[9] 196 USPQ 209 (CCPA 1977).

effective filing date[10]. When the claimed invention is a method of treatment of a disease, the test is "effectiveness to some extent" in alleviating any of the adverse effects of the disease in a person suffering therefrom. Even a *de minimis* extent is sufficient (Id.).

The test is not "safety and efficacy" as required for marketing approval from the Food and Drug Administration. The test is not "clinical efficacy."[11] It is *de minimis* effectiveness in the eyes of the person of skill in the pertinent art on the effective filing date of the application[12].

The courts and the Patent Office have settled that clinical safety and efficacy of therapeutics, avoiding the possibility of a misled public, and any of a number of other worthwhile goals that might be appropriate to consider when new technologies arise, are not concerns of the Patent Office. These concerns are within the jurisdictions of other agencies, such as the Food and Drug Administration, the Department of Agriculture, the Environmental Protection Agency, the Securities and Exchange Commission and similar agencies of the several states.

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[10] E.I. duPont DeNemours and Co. v. Berkeley and Co., supra.

[11] In re Malachowski, 530 F.2d 1402, 189 USPQ 432 (CCPA 1976); In re Langer, 503 F.2d 1380; 183 USPQ 288 (CCPA 1974); In re Anthony, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); In re Hartop, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); In re Krimmel, 130 USPQ 215 (CCPA 1961).

[12] Except in a rare instance where the Examiner can establish that the person of skill in the pertinent art, as of the effective filing date of the application at issue, would require evidence of clinical efficacy before believing that the described treatment would likely have *de minimis* effectiveness.

THE LEGAL STANDARD HAS BEEN MET

NONE OF THE CITED REFERENCES SHOW INOPERABILITY OF MONOCLONAL ANTIBODIES IN THERAPY INVOLVING INHIBITION OF T CELL PROLIFERATION OR PREVENTION OF CD28 AND B7 BINDING

Dillman, Hird, and Osband disclose the use of monoclonal antibodies in the context of cancer (Harris at page 43; Dillman at page 592, left column, first sentence; Dillman at page 592, left column, fifth full paragraph; Dillman at page 591, sentence bridging left and right columns; Dillman at page 594, right column, second full sentence; Dillman at page 594, right column, third full sentence, first paragraph; Dillman at page 594, right column, first paragraph, fourth full sentence; Dillman at page 594, right column, first full paragraph; Dillman at page 597, right column, first full paragraph; Hird at page 185, second full paragraph, fourth sentence; Hird at page 189; Osband at page 193, left column, abstract, second sentence; Osband at page 194, left column, second and third full paragraph).

None of the claims are directed to cancer treatment. The claims in the present application are directed to modulation of an immune response.

Only Waldman discloses the use of monoclonal antibodies on modulation of the immune response (Waldmann at page 1654, abstract; page 1657, right column, first and second full paragraphs). In this regard Waldman teaches that monoclonal antibodies that recognize surface molecules that facilitate cell-cell interactions are also effective immunosuppressive agents (Waldmann at page 1658, left column, third full paragraph).

Applicants respectfully disagree with the Patent Office's

assessment that these cited references show inoperability of the use of monoclonal antibodies in therapy. They certainly do not show the inoperability of the use of fusion proteins in therapy.

At most the cited references point out that monoclonal antibodies have limited use in **cancer** therapy. However, as Thorpe, Dillman, and Hird point out, limited success of a drug does not in turn mean the inoperability thereof. Moreover, as Waldman points out, monoclonal antibodies that recognize surface molecules are effective immunosuppressive agents.

Applicants' discovery to use monoclonal antibodies and fusion proteins in the claimed methods is not speculative, abstruse or esoteric in nature that it must inherently be considered unbelievable, incredible, or factually misleading. For example, some claims involve prevention of CD28 and B7 binding. Applicants provide data supporting this claim, infra.

The Thorpe reference does not teach the non-operability of the use of monoclonal antibodies in therapy. In fact, Thorpe demonstrates that applicants' assertion does not run counter to what would be believed by the ordinary person in the art (Thorpe et al., supra).

Applicants take the position that the Patent Office has not established, on the basis of technical information from the cited references, that the operability of the invention as described in the application would have been regarded as "incredible" by the person of skill in the pertinent art on the effective filing date

of the application.[13]

APPLICANTS PROVIDED IN VITRO DATA SHOWING PRACTICALITY AND ATTAINMENT OF THE DISCLOSED UTILITIES

Applicants respectfully contend that in vitro activity provides **a reasonable correlation** between the disclosed in vitro activity and an in vivo utility. In fact, it is well recognized in the clinical pharmacology arts that in vitro pharmacological studies will enable some assessment to be made of effects likely to be observed in vivo (Sechzer, The Role of Animals in Biomedical Research "The use of short term in vitro and submammalian tests as alternatives to large scale animal bioassays" (1983) The New York Academy of Sciences, at pages 68-73, 68 which will be provided shortly; Long-term animal studies, their predictive value for man, edited by Stuart R. Walker and Anthony D. Dayan, 1986, Chapter 1.3, pages 17-22, which will be provided shortly).

APPLICANTS' DATA ESTABLISH THAT CLAIMED METHODS ARE PREDICTABLE

Further, applicants have shown the following utilities. For example, Figure 6 is a bar graph demonstrating the effect of anti-CD28 and anti-B7 mAbs on T cell proliferation as described in Example 2 (specification at page 9, line 16-19).

Figure 8 is a line graph showing the effect of anti-CD28 and

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[13] In re Marzocchi, 439 F.2d 220, 169 USPQ 367 (CCPA 1971); In re Gazave, 379 F.2d 973, 154 USPQ 92 (CCPA 1967); In re Isaacs, 347 F.2d 887, 146 USPQ 193 (CCPA 1965); Ex parte Rubin, 5 USPQ2d 1461 (BPAI 1987). See also In re Bundy, 209 USPQ 48 (CCPA 1981) and In re Chilowsky, 229 F.2d 457, 108 USPQ 321 (CCPA 1956).

anti-B7 mAbs on the T_h-induced production of immunoglobulin by B cells as described in Example 2 (Figure 8a shows IgM production, Figure 8b shows IgG production).

Figure 11 depicts the results of FACS^R analysis binding of the B7Ig and CD28Ig fusion proteins to transfected CHO cells as described in Example 3.

Figure 12 is a graph illustrating competition binding analysis of ^{125}I-labeled B7Ig fusion protein to immobilized CD28Ig fusion protein as described in Example 3.

Figure 13 is a graph showing the results of Scatchard analysis of B7Ig fusion protein binding to immobilized CD28Ig fusion protein as described in Example 3.

Figure 14 is a graph of FACS^R profiles of B7Ig fusion protein binding to PHA blasts as described in Example 3.

Figure 15 is an autoradiogram of ^{125}I-labeled proteins immunoprecipitated by B7Ig as described in Example 3.

Figure 16 is a graph showing the effect of B7Ig binding to CD28 on CD28-mediated adhesion as described in Example 3.

Applicants teach that administration of the B7 antigen will result in effects similar to the use of anti-CD28 monoclonal antibodies (mAbs) reactive with the CD28 receptor in vivo. Thus, because anti-CD28 mAbs may exert either stimulatory or inhibitory effects on T cells, depending, in part, on the degree of crosslinking or "aggregation" of the CD28 receptor (Damle, J. Immunol. 140:1753-1761 (1988); Ledbetter et al., Blood

75(7):1531-1539 (1990)). It is expected that the B7 antigen, its fragments and derivatives, will act to stimulate or inhibit T cells in a manner similar to the effects observed for an anti-CD28 monoclonal antibody, under similar conditions in vivo (specification at page 22, lines 1-9).

For example, administration of B7 antigen, e.g. as a soluble B7Ig fusion protein to react with CD28 positive T cells, will bind the CD28 receptor on the T cells and result in inhibition of the functional responses of T cells. Under conditions where T cell interactions are occurring as a result of contact between T cells and B cells, binding of introduced B7 antigen in the form of a fusion protein that binds to CD28 receptor on CD28 positive T cells should interfere, i.e. inhibit, the T cell interactions with B cells. Likewise, administration of the CD28 antigen, or its fragments and derivatives in vivo, for example in the form of a soluble CD28Ig fusion protein, will result in binding of the soluble CD28Ig to B7 antigen, preventing the endogenous stimulation of CD28 receptor by B7 positive cells such as activated B cells, and interfering with the interaction of B7 positive cells with T cells (specification at page 21, lines 26-32).

Alternatively, based on the known effects of aggregating the CD28 receptor, either by reacting T cells with immobilized ligand, or by crosslinking as described by Ledbetter et al., Blood 75(7):1531-1539 (1990)), the B7 antigen, and/or its fragments or derivatives, may be used to stimulate T cells, for example by immobilizing B7 antigen or B7Ig fusion protein, for reacting with the T cells. The activated T cells stimulated in this manner in vitro may be used in vivo in adoptive therapy (specification at page 22, lines 1-10).

Therefore, the B7 antigen and/or fragments or derivatives of the antigen may be used to react with T cells to regulate immune responses mediated by functional T cell responses to stimulation of the CD28 receptor. The B7 antigen may be presented for reaction with CD28 positive T cells in various forms. Thus, in addition to employing activated B cells expressing the B7 antigen, the B7 antigen may be encapsulated, for example in liposomes, or using cells that have been genetically engineered, for example using gene transfer, to express the antigen for stimulation of the CD28 receptor on T cells (specification at page 22, lines 11-21).

The CD28 receptor, and/or its fragments or derivatives, may also be used to react with cells expressing the B7 antigen, such as B cells. This reaction will result in inhibition of T cell activation, and inhibition of T cell dependent B cell responses, for example as a result of inhibition of T cell cytokine production (specification at page 22, lines 23-29).

In an additional embodiment of the invention, other reagents, such as molecules reactive with B7 antigen or the CD28 receptor are used to regulate T and/or B cell responses (specification at page 20, lines 34-35; page 21, lines 1-30; page 22, lines 1-32).

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

At page 4 of the Office Action, paragraph 25, the Patent Office objected to the specification under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide an adequate written description of the invention and for failing to adequately teach how to make and/or use the invention, i.e., for failing to provide an enabling disclosure. Further, at paragraph 30 of the

Office Action, the Patent Office rejected claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42, and 78 under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Applicants respectfully traverse the rejection for the reasons that follow.

The essence of the rejection is that the monoclonal antibodies are inoperable in a therapeutic setting. Therefore, applicants could not have shown how to use the claimed invention.

THE LEGAL STANDARD FOR ENABLEMENT

The legal standard is whether applicants have taught how to make and use the claimed invention without undue experimentation[14]. The truth and accuracy of statements in a patent application are presumed unless the Patent Office can establish that the statements are otherwise.

APPLICANTS HAVE MET THE LEGAL STANDARD

APPLICANTS TEACH HOW TO USE THE CLAIMED METHOD IN VITRO

Using monoclonal antibodies and fusion proteins directed separately to B7 and CD28 antigens in an adhesion assay, applicants have discovered that B7 is the natural counter receptor for CD28 and vice versa. Moreover, the B7 antigen, and/or its fragments or derivatives, may be used to stimulate T cells. CD28Ig fusion protein when bound to B7 antigen **on B**

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[14] In Re Eynde, 480 F2d 1364, 178 USPQ 470 (CCPA 1970).

cells, prevents the endogenous stimulation of CD28 receptor by B7 positive cells such as activated B cells, and interferes with the interaction of B7 positive cells with T cells. Further, soluble CD28Ig and B7Ig fusion proteins block T cell proliferation in graft versus host (GVH) disease which accompanies allogeneic bone marrow transplantation. B7Ig stimulates T cell proliferation (Table 3) (specification at page 9,lines 16-19, lines 27-30; page 10, lines 5-25; page 20, lines 34-35; page 21, lines 1-30; page 22, lines 1-32; page 23, lines 3-18; lines 33-35; page 24, lines 1-35; page 25, lines 1-23; page 26, lines 20-35; page 27,lines 1-4, lines 19-36; page 28, lines 1-10; page 37, lines 29-35; pages 38-44, pages 46-51; page 56, lines 14-35; page 57, lines 1-12; pages 59-72).

PARAGRAPH 25(A)

Applicants have disclosed to one of ordinary skill in the art how to use the claimed invention (specification at page 9,lines 16-19, lines 27-30; page 10, lines 5-25; page 20, lines 34-35; page 21, lines 1-30; page 22, lines 1-32; page 23, lines 3-18; lines 33-35; page 24, lines 1-35; page 25, lines 1-23; page 26, lines 20-35; page 27,lines 1-4, lines 19-36; page 28, lines 1-10; page 37, lines 29-35; pages 38-44, pages 46-51; page 56, lines 14-35; page 57, lines 1-12; pages 59-72 and generally throughout).

In view of this teaching it would not require undue experimentation where the skilled artisan to practice applicants' claimed invention from what has been disclosed.

PARAGRAPH 25(B)

The disclosure does provide a sufficient enabling description to

use the claimed invention in vivo.

Applicants provide in vitro data which may be used to design in vivo protocols. It is well recognized in the clinical pharmacology arts that in vitro pharmacological studies will enable some assessment to be made of effects likely to be observed in vivo (Sechzer, The Role of Animals in Biomedical Research "The use of short term in vitro and submammalian tests as alternatives to large scale animal bioassays" (1983) The New Academy of Sciences, at pages 68-73, 68 which will be provided shortly; Long-term animal studies, their predictive value for man, edited by Stuart R. Walker and Anthony D. Dayan, 1986, Chapter 1.3, pages 17-22, which will be provided shortly).

PARAGRAPH 25(C)

The disclosure provides more than a description of B7 antigen on CHO cells. However, applicants will not address this issue further since it is irrelevant because the claimed invention is not directed to using immobilized B7.

PARAGRAPH 25(D)

Applicants respectfully point out that whether or not applicants' disclosure provides an enabling description of a method having the steps of reacting B-cells with T-cells is irrelevant since the claimed invention is not directed to reacting B-cells with T-cells.

PARAGRAPH 25(E)

Applicants respectfully traverse the Patent Office's position that applicants' disclosure does not provide an enabling description of fusion proteins having at least a portion of the extracellular domain of the CD28 receptor. As the Patent Office pointed out at page 5, lines 5-10 of Paper No. 29, the disclosure provides a description of a fusion containing amino acid residues of the CD28 receptor from about amino acid position number 1 to about amino acid position number 134 and a second amino acid sequence corresponding to the hinge, CH2, and CH3 regions of human IgG-1 constant domains. This is a fusion protein having at least a portion of the extracellular domain of the CD28 receptor.

PARAGRAPH 25(F)

Contrary to the Patent Office's position, applicants' specification does not support a method of inhibiting T-cell proliferation with a B7 antigen derivative. For example, figure 16 is a graph showing the effect of B7Ig binding to CD28 on CD28-mediated adhesion as described in Example 3 of the specification. Additionally, the specification provides an enabling description of the use of anti-CD28 antibody in a method of inhibiting T-cell proliferation (specification at page 22, lines 1-9).

PARAGRAPH 25(G)

Applicants' specification does support the scope of claims directed to a method for preventing the binding to the CD28 receptor to the B7 antigen so as to inhibit functional T cell response (specification at page 9,lines 16-19, lines 27-30; page 10, lines 5-25; page 20, lines 34-35; page 21, lines 1-30; page 22, lines 1-32; page 23, lines 3-18; lines 33-35; page 24, lines

1-35; page 25, lines 1-23; page 26, lines 20-35; page 27,lines 1-4, lines 19-36; page 28, lines 1-10; page 37, lines 29-35; pages 38-44, pages 46-51; page 56, lines 14-35; page 57, lines 1-12; pages 59-72).

Contrary to the Patent Office's statements, before applicants, no one had shown that monoclonal antibody 9.3 inhibits binding of B7 to CD28. Others, like Ledbetter et al. infra, showed that antibody 9.3 binds CD28 thereby resulting in T-cell activation and proliferation.

PARAGRAPH 25(H)

Applicants respectfully point out that the issue of "how the methods of claims 9, 10, 15, 17, 35, and 38 will result in inhibiting T-cell proliferation" is irrelevant under 35 U.S.C. §112, first paragraph. 35 U.S.C. §112, first paragraph requires only that applicants teach how to make and use the claimed invention. Applicants teach how to make and use the claimed invention and their data supports the claim (specification at page 9,lines 16-19, lines 27-30; page 10, lines 5-25; page 20, lines 34-35; page 21, lines 1-30; page 22, lines 1-32; page 23, lines 3-18; lines 33-35; page 24, lines 1-35; page 25, lines 1-23; page 26, lines 20-35; page 27,lines 1-4, lines 19-36; page 28, lines 1-10; page 37, lines 29-35; pages 38-44, pages 46-51; page 56, lines 14-35; page 57, lines 1-12; pages 59-72).

PARAGRAPH 25(I)

Applicants respectfully traverse the Patent Office's position that the specification does not enable a method for inhibiting proliferation using an intact antibody molecule to the CD28

receptor. Figure 6 is a bar graph demonstrating the effect of anti-CD28 and anti-B7 mAbs on T cell proliferation as described in Example 2 of the application (specification at page 9, line 16-19).

PARAGRAPH 25(J)

Whether or not the specification contemplates the CTLA4 molecule is irrelevant to the claimed invention. The claims are directed to CD28/B7 interaction and the inhibition of T-cell proliferation. The claimed invention is not directed to inhibiting T-cell proliferation using all possible pathways.

A HOMOLOGOUS MOLECULE WAS USED IN VIVO

The courts have on several occasions found evidence of structural similarity to known compounds with particular therapeutic or pharmcological uses as supporting therapeutic utility of a newly claimed compound[15]. It appears that it will be Patent Office policy that such evidence, when provided by an applicant in support of an assertion of utility, be given appropriate weight in determining whether one skilled in the art would find the asserted utility credible (Proposed Utility Examination Guidelines published in the January 30, 1995 edition of the Federal Register, Section III(B)).

CD28 and CTLA4 are homologous molecules. Although different from CTLA4, CD28 shares with it some structural features, such as the precise number and relative position of cysteines, and a proline-rich stretch near the hydrophobic portion (Brunet et al.,

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[15] In re Jolles, infra.

Immunol. Rev. 103:21-36, 30 (1988), which will be provided shortly). However, this does not mean that they render each other obvious in terms of their specific amino acid sequences. This simply means that CTLA4 has predictive value for determining the behavior of soluble CD28 in vivo, i.e., CD28 or CD28Ig can bind the B7 antigen and at a higher concentration than CTLA4, soluble CD28 can block CTLA4 from binding the B7 antigen.

Applicants brought the Lenschow reference to the Patent Office's attention to show that *in vitro* data with a homologous molecule correlates with *in vivo* results obtained with that molecule (specification at page 21, lines 1-9 and page 24, lines 6-12). D. Lenschow et al. ((1992) Science 257:789-792 entitled "Long Term Survival of Xenogeneic Pancreatic Islet Grafts Induced by CTLA4Ig" already of record) provided *in vivo* data in mouse showing CTLA4Ig blocked the CD28 receptor from binding the B7 antigen results in manipulating the mouse immune system into accepting transplanted tissue instead of attacking it and thereby preventing the rejection of transplanted tissue.

Since CTLA4 and CD28 are homologous molecules, and applicants have shown that CTLA4 is operable in vivo, there is no basis to the rejection that applicants failed to teach how to use the claimed methods in vivo.

REJECTION UNDER 35 U.S.C. §102(B)

At page 6 of the Office Action, paragraph 28, the Patent Office rejected claim 37 under 35 U.S.C. § 102(b) as allegedly anticipated by Ledbetter et al. (1985). The Patent Office stated that Ledbetter et al. teach Fab fragments of anti-TP44 (CD28) were ineffective in inducing T-cell proliferation. The Patent

Office stated that these antibody fragments will inherently block the interaction between CD28 and B7. The Fab fragment is derived from monoclonal antibody 9.3.

Applicants respectfully traverse the rejection for the reasons which follow.

Ledbetter et al. teach that anti-Tp44 (also known as anti-CD28) augments T cell proliferation thereby sustaining T cell growth over an extended period of time (Ledbetter at page 2334, left column, third paragraph; page 2331, right column, first full paragraph, lines 5-8 and page 2332, right column, last paragraph). The Fab fragment of the anti-Tp44 antibody did not augment proliferation (Ledbetter at page 2333, right column, lines 5-7).

This is not suggestive of or anticipative of the claimed invention, i.e., preventing CD28 and B7 binding using anti-CD28 antibodies. Before applicants' invention, no one knew that CD28 bound B7 and vice versa.

The Patent Office's assertion of inherency is unsupported and constitutes impermissible hindsight and speculation. Ledbetter teaches T cell proliferation. The claimed invention is directed to inhibition of functional T cell responses.

Inherency must be certain[16]. Inherency may not be established by probabilities or possibilities. The mere fact that a product

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[16] Ex parte Cyba, 155 U.S.P.Q 756 (Pat. Off. Bd. App. 1966).

may result from a given set of circumstances is not sufficient[17]. The fact that the Fab fragment of the anti-Tp44 antibody did not augment proliferation does not mean T cell proliferation was inhibited. It may have been that the Fab fragment was functionally inactive (Ledbetter at page 2335, left column, first paragraph, lines 5-6).

Anticipation of inventions set forth in product claims cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references[18]. Therefore, the rejection of the claims based on Ledbetter et al. for anticipation or obviousness is improper and should be withdrawn.

DOUBLE PATENTING

At paragraph 30, the Patent Office rejected claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42, and 78 as allegedly directed to an invention not patently distinct from claims 1-24 of U.S. Serial No. 08/076,071.

Applicants respectfully traverse the rejection as claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42, and 78 are patently distinct from claims 1-24 of U.S. Serial No. 08/076,071.

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[17] Ex parte Skinner, 2 U.S.P.Q.2d 1788 (Bd. Pat. App. & Inter. 1986).

[18] W.L. Gore & Associates, Inc. v. Garlock, Inc. 220 U.S.P.Q. 303, 314 (Fed. Cir. 1983).

OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

The Patent Office rejected claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42, and 78 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-24 of copending application U.S. Serial No. 08/076,071.

Applicants may provide a terminal disclaimer at the appropriate time, i.e., when the Patent Office allows overlapping claims in the subject application or U.S. Serial No. 08/076,071.

REJECTION UNDER 35 U.S.C. §103

CLAIMS 1, 3, 5-8, 18, 41 AND 42

At page 7 of the Office Action, paragraph 32, the Patent Office rejected claims 1, 3, 5-8, 18, 41 and 42 under 35 U.S.C. § 103 as allegedly unpatentable over Linsley et al. (1990) and Freeman et al. (1989) in view of Capon et al. for reasons of record.

Applicants respectfully traverse the rejection. The subject application is a file wrapper continuation application of U.S. Serial No. 722,101, filed June 27, 1991, which is a continuation-in-part of U.S. Serial No. 547,980, filed July 2, 1990, now abandoned, which was a continuation-in-part of U.S. Serial No. 498,949, filed March 26, 1990, now abandoned.

The Linsley reference was published after U.S. Serial No. 498,949, filed March 26, 1990.

The related parent applications teach how to make and use the rejected claims in accordance with 35 U.S.C. §112, first

paragraph.

For example, the related applications teaches the following:

(1) the CD28 antigen recognizes and binds the B7 antigen expressed by activated B cells (U.S. Serial No. 498,949 at page 4, lines 10-13; U.S. Serial No. 547,980 at page 4,lines 21-25);

(2) the CD28 antigen, its fragments or derivatives are reacted with B cells to regulate T cell/B cell interactions (U.S. Serial No. 498,949 at page 4, lines 14-15; U.S. Serial No. 547,980 at page 4,lines 25-26);

(3) antibodies or other molecules reactive with the CD28 antigen or the CD28 ligand may be used to inhibit interaction of CD28 antigen with its ligand, may be used to inhibit interaction of CD28 antigen with its ligand, thereby regulating T cell/B cell interactions (U.S. Serial No. 498,949 at page 4, lines 16-19; U.S. Serial No. 547,980 at page 4,lines 27-28);

(4) a method for regulating CD28 specific T cell/B cell interactions by reacting T cells with a CD28 ligand reactive with CD28 antigen, the ligand being expressed on the surface of B cells and comprising the B7 antigen (U.S. Serial No. 498,949 at page 4, lines 20-24; U.S. Serial No. 547,980 at page 4, lines 32-35); and

(5) a method for regulating immune responses by contacting T cells with fragments containing at least a portion of the extracellular domain of the CD28 ligand (U.S. Serial No. 498,949 at page 4, lines 25-30; U.S. Serial No. 547,980 at page 5, lines 1-5).

Applicants' own earlier work is not prior art as to him[19] Priority has been properly claimed from related applications, U.S. Serial No. 498,949 and U.S. Serial No. 547,980. The attention of the Patent Office is respectfully directed to the cross-references at page 1 of applicants' Preliminary Amendment Submitted in connection with the Accompanying File Wapper Continuation Application Filed under 37 C.F.R. §1.62 claiming the benefit under 35 U.S.C. § 120 of these related applications. The effect of §120 is clearly to entitle applicants to the effective filing date of March 26, 1990 for any subject matter disclosed in U.S. Serial No. 498,949. As such, the Linsley reference is improperly cited as prior art and should be withdrawn.

Therefore, applicants respectfully traverse this rejection and request that it be withdrawn as contrary to the provisions of §120.

Further, applicants traverse the Patent Office's rejection that "from the combined teachings of Freeman and Capon, a soluble B7Ig fusion protein would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention was made for the following reasons.

Applicants' invention lies in the discovery that B7 binds CD28.

The claimed methods cannot be prima facie obvious since no one had identified the B7 counter receptor before applicants. There would have been no motivation in the prior art at the time of the

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[19] Corning Glass Works v. Brenner, 1972, 470 F.2d 410, 512 U.S. App. D.C. 262.

invention to use the method of Capon et al. to make chimeric constructs using the extracellular domain of B7 antigen of Freeman for which the counter receptor was unknown. In particular, there would have been no motivation in the prior art to construct chimeric B7Ig molecules for any purpose except to investigate further what B7 would have been useful for.

There must be a reason or suggestion in the art for selecting which extracellular domain to use other than the knowledge learned from applicants' disclosure[20]. However, the cited references provide none.

The Patent Office has proposed the modification himself, ***after*** reading the present application. This is purely hindsight reconstruction of the claimed invention, and is impermissible under the controlling decisions of the Court of Appeals for the Federal Circuit.

> In our view, however, such proposed modification amounts to a hindsight reconstruction of the prior art patents in order to arrive at appellant's invention. Without having the benefit of appellant's disclosure . . . the artisan would [not] have found it obvious . . .
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> . . . We have carefully reviewed the [cited] references in their entireties, and we find ***no express or implied suggestion in the collective teachings which would have motivated the artisan to combine them in the manner proposed*** (emphasis added)[21].

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[20] In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988).

[21] Ex parte Dussand, 7 U.S.P.Q. 2nd 1818, 1820.

1. THE REJECTION IS BASED ON FACTUALLY FALSE ASSUMPTIONS

The Patent Office's position is that the combination of Capon et al. and Freeman et al. teach that one would be motivated to produce B7Ig to regulate activation of B cells, and second, one would be motivated to construct B7Ig in order to detect the B7 receptor.

This reasoning falsely assumes (1) that there is some similarity between B7 and CD4 which would suggest their interchangeability; and (2) that there is motivation to produce B7Ig so as to regulate activity of B cells; and (3) that motivation exists to produce B7Ig so as to discover the B7 receptor, should it exist. Applicants respectfully reject these arguments.

2. THE REJECTION IS BASED ON INAPPLICABLE LEGAL STANDARDS

In rejecting the claimed methods, the Patent Office acted contrary to the guidance provided by the Federal Circuit as to how to evaluate obviousness with respect to the prior art.

In order for an obviousness rejection to be proper, the prior art itself must suggest the desirability of making the required modification or combination. As the Court of Appeals for the Federal Circuit has held:

> The mere fact that the prior art could be so modified would not have made the modification obvious unless the ***prior art suggested the desirability of the modification*** (emphasis added)[22].

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[22] In re Gordon, 221 U.S.P.Q. 1125, 1127.

Here, no such suggestion is presented by the cited publications. It could not have been suggested because before applicants' invention no one knew that a B7 counter receptor existed.

3. THERE IS NO SUGGESTION TO COMBINE THE REFERENCES

There was no knowledge of the existence of a B7 counter receptor. Therefore, there was no motivation to substitute a claimed compound (B7) for the prior art compound (CD4) unless the two compounds shared a common utility[23].

A. CD4 AND B7 DO NOT SHARE A COMMON UTILITY

CD4 and B7 do not share a common utility. Freeman teaches that CD4 recognizes and binds gp120 and thus is involved in modulating HIV infection (Freeman at page 2714).

B. B7 AND CD4 ARE NOT SIMILAR PROTEINS

SEQUENCE SIMILARITY BETWEEN CD4 AND B7 ARE LESS THAN THREE AMINO ACIDS

First, there is no similarity in function, structure, or any other property between CD4 and B7 (The Leucocyte Antigen Facts Book (1993) Barclay et al. (eds.) at pages 110-111 and pages 276-277 which will be provided shortly). In fact, there are no homologous regions of greater than three amino acids which are shared by CD4 and B7.

Because B7 and CD4 are not similar proteins, the findings about

the structure of CD4 have little, if any, predictive value for determining the behavior of B7. By the Patent Office's reasoning, any molecule of the Ig superfamily could substitute for any other member, even those with a different number of domains; a different arrangement of domains; or a different number of arrangement of disulfide bonds. This is contrary to what is known about the specificity and function of these molecules which depend on their three dimensional structure (Linsley et al., J. Exp. Med. 173:721-730 (1991) which will be provided shortly).

THERE IS NO EQUIVALENT SHOWING THAT THE FUNCTIONAL DOMAINS CAN BE INTERCHANGED THROUGHOUT THE IMMUNOGLOBULIN SUPERFAMILY

As applicants have argued previously, there is no equivalent showing that the functional domains can be interchanged throughout the immunoglobulin superfamily, whose members vary widely in structure. In fact, applicants data show that functional domains cannot be interchanged within the immunoglobulin superfamily without a loss in affinity and specificity (Linsley et al., J. Exp. Med. 173:721-730 (1991)).

Before applicants' invention, no one had identified the ligand which binds B7 or B7's function. Applicants were the first to discover that B7 recognizes and binds CD28 and CTLA4 antigens. Because it binds such antigens, B7 is involved in modulating CTLA4/B7 and/or CD28/B7 antigen-mediated T cell responses.

The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested

the desirability of the modification[24]. The question is not simply whether the prior art teaches the particular element of the invention, but whether it would suggest the desirability, and thus the obviousness, of making the combination[25].

Without suggestion or motivation to produce the B7Ig, one is merely picking and choosing among the individual elements of assorted prior art references to recreate the claimed invention. It is well established in patent law that this practice is impermissible to establish obviousness[26].

For these reasons, applicants respectfully contend that the cited references did not provide or suggest a motivation to produce the claimed invention. Therefore, the cited references fail alone or in combination to render obvious the claimed invention.

4. WITHOUT KNOWING THE LIGAND FOR THE CLAIMED B7Ig THE MOTIVATION FOR THE COMBINATION WOULD HAVE BEEN FOR USE TESTING ONLY

Freeman teaches only that "B7 expression was confined to several histologically defined subgroups of B cell malignancies" (Freeman at page 2714, abstract). However, this finding by itself is not significant, i.e., B7 is not a marker for B cell malignancy. B7 is not specifically expressed on neoplastic B lymphocytes but are also expressed on activated B lymphocytes (Freeman at page 2714,

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[24] In re Laskowski, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989).

[25] Carella v. Starlight Archery, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986).

[26] Smithkline Diagnostics, Inc. v. Helena Laboratories Corp., 859 F.2d 878, 887, 8 USPQ2d 1468, 1475 (Fed. Cir. 1988).

second column, second full paragraph).

In contrast to the teaching in the prior art, B7 regulates a ***T cell*** response, not a B cell response. Thus, the Patent Office's contention that there was motivation to construct B7Ig to regulate activation of B cells is improper because it could not have been used to regulate activation of B cells.

5. THE MOTIVATION FOR PRODUCING CLAIMED MOLECULE AS AN OBJECT OF USE TESTING IS PROSCRIBED BY CASE LAW.

Applicants respectfully contend that the motivation of using the claimed invention to identify the B7 counter receptor is making the claimed B7Ig the object of use testing[27]. Combining references so as to render a claimed invention obvious for use testing only, i.e. to determine its counter receptor and its potential use is not proper motivation for combining references. If such motivation was proper then it should not be possible to obtain a patent for a new composition including as one ingredient an old compound[28]. Clearly, this is not the law. Patents can be and are rewarded for new compositions including old compounds.

In summary, applicants respectfully contend that the claimed invention is not obvious in view of the cited references.

In view of the aforementioned discussion, applicants respectfully request that the Patent Office reconsider and withdraw the rejection of the claims under 35 U.S.C. §103.

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[27] Brenner v. Manson, supra.

[28] In re Wiggins, 396 F.2d 356, 158 USPQ 199 (CCPA 1968).

CLAIMS 19, 39, 40 and 78

The Patent Office rejected claims 19, 39, 40 and 78 under 35 U.S.C. § 103 as allegedly unpatentable over Linsley et al. (1990) and Aruffo et al. (1987) in view of Capon et al. for reasons of record.

Applicants respectfully traverse the rejection for the same reasons set forth hereinabove concerning the Linsley, Freeman, and Capon references. Applicants' own earlier work is not prior art as to him[29]. The Linsley reference is not prior art and should properly be withdrawn. Applicants are entitled under 35 U.S.C. §120 to the effective filing date of March 26, 1990 for any subject matter disclosed in U.S. Serial No. 498,949.

Further, for the record applicants traverse the Patent Office's rejection that "from the combined teachings of Aruffo and Capon, a soluble CD28Ig fusion protein would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention was made for reasons similar to those set forth supra concerning B7Ig.

1. THE REJECTION IS BASED ON FACTUALLY FALSE ASSUMPTIONS

The essence of the rejection is that it would have been obvious to combine the extracellular portion of CD28 with human Ig because Capon teaches CD4 Ig.

This reasoning falsely assumes that there is some similarity

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[29] Corning Glass Works v. Brenner, 1972, 470 F.2d 410, 512 U.S. App. D.C. 262.

between CD28 and CD4 which would suggest their interchangeability.

Applicants respectfully reject both these arguments.

ANY REGION OF SEQUENCE SIMILARITY BETWEEN CD4 AND CD28 ARE LESS THAN THREE AMINO ACIDS

First, there is no similarity in function, structure, or any other property between CD4 and CD28 (The Leucocyte Antigen Facts Book (1993) Barclay et al. (eds.) at pages 110-111 and pages 162-163 which will be provided shortly). In fact, there are no homologous regions of greater than about three amino acids which are shared by CD4 and CD28. The Patent Office is respectfully reminded that the sizes of epitopes for protein or peptide antigens are typically about 9 to 15 amino acids (I. Wilson et al., "The Structure of an Antigenic Determinant", Cell 37:767-778 (1984) which will be provided shortly). Therefore, the short (less than three) amino acid similarity is insignificant.

CD28 AND CD4 ARE NOT SIMILAR PROTEINS

Because CD28 and CD4 are not similar proteins, the findings about the structure of CD4 have little, if any, predictive value for determining the behavior of CD28. By the Patent Office's reasoning, any molecule of the Ig superfamily could substitute for any other member, even those with a different number of domains; a different arrangement of domains; or a different arrangement of domains of disulfide bonds. This is contrary to what is known about the specificity and function of these molecules which depend on their three dimensional structure (Linsley et al., J. Exp. Med. 173:721-730 (1991) which will be

provided shortly).

THERE IS NO EQUIVALENT SHOWING THAT THE FUNCTIONAL DOMAINS CAN BE INTERCHANGED THROUGHOUT THE IMMUNOGLOBULIN SUPERFAMILY

As applicants have argued previously, there is no equivalent showing that the functional domains can be interchanged throughout the immunoglobulin superfamily, whose members vary widely in structure. In fact, applicants' data show that functional domains cannot be interchanged within the immunoglobulin superfamily without a loss in affinity and specificity (Linsley et al., J. Exp. Med. 173:721-730 (1991)).

The rejection of the Patent Office appears to be contrary to the guidance provided by the Federal Circuit as to how references can be combined for the reasons set forth supra. concerning B7Ig.

2. BECAUSE THE FUNCTION OF CD28 WAS UNKNOWN, THERE WOULD HAVE BEEN NO SUGGESTION TO COMBINE THE REFERENCES

There would have been no motivation to substitute CD28 for the prior art compound (CD4) unless the two compounds share a common utility (*In re Lalu and Foulletier*)[30]. The function of CD28 was unknown (specification at page 7, line 15). Therefore, there could not have been any motivation for substituting CD28 with CD4.

CD4 AND CD28 DO NOT SHARE A COMMON UTILITY

CD4 and CD28 do not share a common utility. CD4 recognizes and binds gp120 and thus is involved in modulating HIV. The function

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[30] 747 F.2D 703, 223 USPQ 1257 (Fed. Cir. 1984).

of CD28 antigen was unknown (specification at page 7, line 15). Before applicants' invention the ligand for the CD28 receptor was unknown (specification at page 1, first full paragraph).

Before applicants' invention, no one had identified the ligand which binds CD28 or CD28's function. Applicants were the first to discover that CD28 recognizes and binds B7 antigen. Because CD28 binds B7 antigen, CD28 is involved in modulating CD28/B7 antigen-mediated T cell responses.

The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification[31]. The question is not simply whether the prior art teaches the particular element of the invention, but whether it would suggest the desirability, and thus the obviousness, of making the combination[32].

Without suggestion or motivation to produce the CD28Ig fusion protein, one is merely picking and choosing among the individual elements of assorted prior art references to recreate the claimed invention. It is well established in patent law that this practice is impermissible to establish obviousness[33].

There must be a reason or suggestion in the art for selecting which extracellular domain to use other than the knowledge

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[31] In re Laskowski, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989).

[32] Carella v. Starlight Archery, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986).

[33] Smithkline Diagnostics, Inc. v. Helena Laboratories Corp., 859 F.2d 878, 887, 8 USPQ2d 1468, 1475 (Fed. Cir. 1988).

learned from applicants' disclosure[34]. The cited references provide none.

For these reasons, applicants respectfully contend that the cited references did not provide or suggest a motivation to produce the claimed invention. Therefore, the cited references fail alone or in combination to render obvious the claimed invention.

In view of these facts applicants respectfully request that the Patent Office withdraw the rejection under 35 U.S.C. §103.

No fee, other than the extension fee, is deemed necessary in connection with the filing of this response. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 13-2724.

Respectfully submitted,

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I hereby certify that this paper is being deposited this date with the U.S. Postal Service as first class mail addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Sarah B. Adriano 1/17/95
Signature Date

[34] In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988).